EXHIBIT P

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/334,115	12/12/2008	Neil P. Desai	638772000402	7612

25226 7590 06/18/2009
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EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
06/18/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/334,115	DESAI ET AL.	
	Examiner	Art Unit	
	JAGADISHWAR R. SAMALA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are pending in the instant application.

Drawings

The drawing(s) filed on 12/12/2008 has been acknowledged.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1, 3, 9, 12-15 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Binaco (US 2004/0047835)

Binaco discloses a composition for treatment of pancreatic cancer comprising paclitaxel and gemicitabine. The drug conjugates can be formed into a core particle having particle size ranging from 0.1 to 200 microns (0018 and 0124). The composition may be prepared as injectables, as liquid solutions comprising protein carrier such as human serum albumin (0107). The composition can be administered in an appropriate dosage forms and treatment regimen provides the agent(s) in an amount sufficient to provide therapeutic benefit i.e., recommended to be used in the treatment of solid tumors (01480160).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al (US 6,506,405) in view of Binaco (US 2004/0047835) and Prendergast (US 2002/0169140).

Applicant claims are drawn to a method of treating pancreatic cancer comprising administering to the individual: a) an effective amount of a composition comprising nanoparticles comprising paclitaxel and a carrier protein, and b) an effective amount of gemicitabine.

Desai discloses a method of administrating a composition comprising anti-cancer drugs (Capxol, a cremophor-free formulation of anticancer drug paclitaxel and human serum albumin) in the form of colloidal suspension (abstract and col. 6 lines 9-13). The

composition comprising paclitaxel and albumin with a particle size in the range of 20-400 nm and free of cremophor (col. 7 lines 1-5). Primary tumors contemplated for treatment includes cancers of pancreas (col. 12 lines 10-13). The method of administering a therapeutically effective amount of taxane in the range of about 30 mg/m^2 to about 1000 mg/m^2 with a treatment cycle no greater than about three weeks (col. 31 lines 12-18). Additional disclosure includes that combination of caprxol formulations are not limited to the use of paclitaxel and may be utilized with a wide variety of pharmacologically active ingredients including anti-infective, other chemotherapeutic agents and the like.

Desai fails to include an effective amount of at least one other chemotherapeutic agent such as gemcitabine in the composition.

Bianco discloses a method and composition comprising drug conjugated to treat a disease associated with undesirable or aberrant cell growth or proliferation, such as cancer (abstract and 0055). The drug conjugates comprising paclitaxel is used in combination with additional chemotherapeutic agent such as gemcitabine (0018). The composition may be prepared as injectables, as liquid solutions (in sterile water or saline) and mixed with physiologically acceptable excipient such as human serum albumin (0107). Additional disclosure includes that conjugated paclitaxels in combination with other drugs, such as chemotherapeutic or anti-proliferative drugs provide distinct advantages over existing compositions for combination drug therapy, particularly for the treatment of cancer. For example, the compositions exhibit reduced toxicity and side effects, thereby allowing combination treatment with higher doses or for

longer time periods as compared to treatment using non-conjugated or non-derivatized drugs.

Prendergast discloses a method of treating cancer comprising administering to a patient in need thereof a combination of pharmaceutically active compound with chemotherapeutic agents (0034-0036). In one embodiment, the chemotherapeutic agent is antimetabolities such as gemcitabine (0045 and claim 17). Prendergast also discloses that gemcitabine is approved for the treatment of locally advanced or metastatic pancreatic cancer with additional activity alone and in combination with other cytotoxic agents (0127). Additional disclosure includes that the pharmaceutical formulation can be administered simultaneously or sequentially, e.g., several days apart or more than a week apart and it is within the skill of the ordinary artisan to select a specific formulation and route of administration and then test suitability for use (0119). All such variations in administration of the combination therapy are within the preview of skilled artisan (For example, no episodes of dose-limiting toxicities were observed at gemcitabine and capecitabine doses of 1,000 and 166 mg/m^2 with metastatic colorectal and pancreatic cancer, Journal of Clinical Oncology, 20, 582-587, 2002).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate additional chemotherapeutic agent (gemcitabine) and ration of carrier protein to the drug into Desai's composition. The person of ordinary skill in the art would have been motivated to make these modifications to prepare compositions comprising additional chemotherapeutic agent and reasonably would have expected success, because paclitaxel composition comprising additional

chemotherapeutic agent as taught by Bianco and Prendergast can be used in same field of endeavor, such as to inhibit proliferation of the cell and improved methods of treating cancer using combination of chemotherapeutic agents in an effort to attack tumor cells through multiple mechanisms and thereby more effectively halt tumor growth and kill tumor cells. “It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose such as for treating pancreatic cancer. [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) MPEP 2144.06. In this instance, it would have been obvious to combine paclitaxel and gemcitabine for additive effect to treat pancreatic cancer, since both drugs have been used to treat pancreatic cancer in the prior art.

The references do not specifically teach the weight ration of the albumin and the paclitaxel in the nanoparticle composition as claimed by Applicant. The amounts or ratio's of albumin and the paclitaxel is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amounts of albumin and paclitaxel in order to achieve the desired results, such as for the preparation of a formulation of paclitaxel that do not cause neurotoxicity, but kills the carcinogenic pancreatic cells. Thus, absent some demonstration of unexpected results from the

claimed parameters, this optimization of weight ration of albumin and the paclitaxel in a composition would have been obvious at the time of Applicant's invention.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1, 4-6, 9-15 and 18 are rejected on the ground of nonstatutory double patenting over claims 1-3, 11, 16-17 and 23-25 of U. S. Patent No. 6,096,331 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: claims are directed to compositions and method useful for the in vivo delivery of a pharmaceutically active anti-cancer agents such as paclitaxel wherein the agent is associated with a polymeric biocompatible material such as albumin and formulation is free of cremophor. The only difference between the instant claims and the patent recited claims is composition comprising an effective amount of at least one other chemotherapeutic agent. It would have been obvious to one of ordinary skill in the art to add second chemotherapeutic agent as suggested by Binaco (US 2004/0047835)

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

3. Claims 1, 4-6, 9-15 and 18 are rejected on the ground of nonstatutory double patenting over claims 1, 3-4, 6-9, 13-17, 33,41, 60 and 65 of U. S. Patent No. 6,506,405 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: claims are directed to compositions and method useful for the in vivo delivery of a pharmaceutically active anti-cancer agents such as paclitaxel wherein the agent is associated with a polymeric biocompatible material such as albumin and formulation is free of cremophor. The only difference between the instant claims and the patent recited claims is composition comprising an effective amount of at least one other chemotherapeutic agent. It would have been obvious to one of ordinary skill in the art to add second chemotherapeutic agent as suggested by Binaco (US 2004/0047835).

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Conclusion

1. No claims are allowed at this time.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAGADISHWAR R. SAMALA whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jake M. Vu/
Primary Examiner, Art Unit 1618

Jagadishwar R Samala
Examiner
Art Unit 1618

sjr